Effective Health Care

Fixed-dose Combination Therapy for Secondary Prevention of CVD

Results of Topic Selection Process & Next Steps

The nominator, the Centers for Disease Control and Prevention (CDC) Million Hearts Initiative, is interested in a new AHRQ review on the effectiveness of fixed-dose combination therapy (ie, fixed dosages of aspirin, BP-lowering medication, and cholesterol-lowering medication) on the secondary prevention of cardiovascular disease (CVD). Due to limited original research addressing the key question, the AHRQ Effective Health Care (EHC) Program will not develop a new review on this topic at this time. No further activity on this topic will be undertaken by the AHRQ EHC Program.

Topic Brief

Topic Name: Centers for Disease Control and Prevention (CDC) Million Hearts Initiative

Topic #: 0723

Nomination Date: October 31, 2016

Topic Brief Date: February 2, 2017

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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Summary of Key Findings:

- Appropriateness and importance: The nomination is both appropriate and important. Although CVD fixed dose-combination therapy delivered as a single pill (ie, the polypill) has not been approved by the FDA, each of the individual drugs have been approved separately.
- Duplication: A new review on this topic would not be duplicative of an existing product. We identified 2 reviews pertinent to the key question; however, these reviews did not include the range of drug delivery options (ie, both as the polypill and separate pills) of interest, nor did they conduct analyses specific to the intervention-comparator pair (fixed-dose combination with aspirin, stain, and ACEI/ARB vs. management by a clinician) of interest.
- Impact: A new review on this topic would have high impact potential, as the value of fixed dose combination therapy for secondary prevention for CVD over management by a clinician is still debated.
- Feasibility: A new AHRQ review on this topic is not feasible at this time.
    - *Size/scope of review:* Our search of PubMed resulted in a total of 157 unique titles. We identified 6 studies (4 RCTs, 1 IPD meta-analysis and 1 cost

analysis) and 2 study protocols of fixed-dose combination therapy delivered as a polypill.

- *Clinicaltrials.gov:* We identified 2 ongoing studies of fixed-dose combination therapy delivered as a polypill.

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Introduction

Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality worldwide.[1] In the United States, one in four deaths is caused by CVD.[2] Patients living with CVD are often prescribed blood pressure-lowering medication, cholesterol-lowering medication, and aspirin alone or in combination. However, long term adherence is poor, which may be contributing to decreased effectiveness of these medications in secondary prevention.[3,4] Fixed-dose combination therapy of these three medications rather than individual titration of each drug has been proposed as both a primary and secondary prevention strategy for CVD, as it could reduce the complexity of taking multiple medications, improve adherence, and lower costs.[5] However, there have been concerns about the safety of prescribing these pills in a fixed-dose combination, because by definition it eliminates the careful monitoring and titration of medications that is currently recommended for CVD patients.[6] There have also been concerns that fixed-dose combination therapy may inadvertently send a message to patients that there is no need to diet, exercise, or manage other important risk factors.[7]

Topic nomination *#0723 Fixed-Dose Combination Therapy for the Prevention of CVD* was received on October 31, 2016. It was nominated by the Centers for Disease Control and Prevention (CDC) Million Hearts Initiative. The original nomination focused on the delivery of fixed-dose combination therapy as a polypill. However, AHRQ's EHC Program typically focuses on reviews that inform healthcare decision-making of interventions available in the U.S. At this time, fixed-dose combination therapy delivered as a polypill is not FDA-approved and not available in the U.S. The individual drugs in each class (aspirin, cholesterol-lowering agent, and blood pressure-lowering agent) are FDA-approved and have been recommended and used for the indications noted above. We spoke to the nominator, and they agreed to focus the scope of the workup to on fixed dose delivery delivered in any form: either as a polypill or as separate pills. Throughout this report, we use the term fixed dose combination therapy" to refer to any intervention that delivers the 3 drugs in fixed-dosage together, regardless of the mode of delivery. We use the term "polypill" to refer to fixed-dose combination therapy delivered as a single pill.

The question for this nomination is:

Key Question 1. For adults with known CVD or at a high risk of developing CVD, what is the effectiveness of a fixed-dose combination therapy (ie, aspirin, cholesterol management, and blood pressure-lowering medication) on clinical outcomes, medication adherence, medication costs, and health care utilization?

To define the inclusion criteria for the key questions we specify the population, interventions, comparators, and outcomes (PICO) of interest. See Table 1.

Table 1. Key Questions and PICOs

Key Questions	1. For adults with known CVD or at a high risk of developing CVD, what is the effectiveness of a fixed-dose combination therapy (ie, aspirin, cholesterol management, and blood pressure-lowering medication) on clinical outcomes, medication adherence, medication costs, and health care utilization?
Population	Adults with known CVD or at a high risk of developing CVD (including those with diabetes)
Intervention	Fixed-dose combination therapy that includes 3 of the following: • **Aspirin** • **Statin** [eg, Lovastatin (Altoprev, Mevacor), Pravastatin (Pravachol), Simvastatin (Zocor), Fluvastatin (Lescol), Atorvastatin (Lipitor), Rosuvastatin (Crestor)] • **ACE inhibitor** [eg, Benazepril (Lotensin), Captopril (Capoten), Enalapril (Vasotec, Epaned), Fosinopril (Monopril), Lisinopril (Prinivil, Zestril, Qbrelis), Moexipril (Univasc), Perindopril (Aceon), Quinapril (Accupril), Ramipril (Altace), Trandolapril (Mavik)] **or ARB** [eg, Candesartan (Atacand), Eprosartan (Teveten), Irbesartan (Avapro), Losartan (Cozaar), Olmesartan (Benicar), Telmisartan (Micardis), Valsartan (Diovan), Azilsartan (Edarbi)]
Comparator	Usual care (eg, each medication is monitored and titrated separately by a clinician using clinical judgment)
Outcomes	• Medication adherence • Clinical outcomes - BP level or BP control - Cholesterol level or cholesterol control - Cardiovascular events including acute MI, acute stroke (ischemic cerebral infarction, hemorrhagic stroke), angina pectoris, transient ischemic attack, and cardiac arrest - CVD conditions such as heart failure, abdominal aortic aneurysms, atheroembolism, atherosclerosis, peripheral artery disease, hypertension, or other cerebrovascular disease or ischemic heart disease • Mortality • Medication costs for patients • Harms (eg, adverse drug events, angioedema, dizziness, falls, myalgia, liver damage, electrolyte disorders, cough, and other symptoms of inadequate control or overtreatment) • Health care utilization (eg, number of health care visits, number of hospitalizations)

Abbreviations: BP=Blood pressure; CVD=Cardiovascular disease; MI=Myocardial infarction

Methods

To assess topic nomination *#0723 Fixed-Dose Combination Therapy for the Prevention of CVD* for priority for a systematic review or other AHRQ EHC report, we used a modified process based on established criteria. Our assessment is hierarchical in nature, with the findings of our assessment determining the need for further evaluation. Details related to our assessment are provided in Appendix A.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new " systematic review or other AHRQ product would be duplicative. "
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance (see Appendix A).

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews pertaining to the key questions of the nomination. Table 2 includes the citations for the reviews that were determined to address the key questions.

Impact of a New Evidence Review

The impact of a new evidence review was assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether a new review could influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a literature search in PubMed from December 2011 to December 2016. We reviewed all identified titles and abstracts for inclusion and classified identified studies by study design, to assess the size and scope of a potential evidence review. See Table 2, Feasibility Column, Size/Scope of Review Section for the citations of included studies.

Value

We assessed the nomination for value (see Appendix A). We considered whether a partner organization could use this evidence review to facilitate evidence-based change; or the presence of clinical, consumer, or policymaking context that is amenable to evidence-based change.

Compilation of Findings

We constructed a table outlining the selection criteria as they pertain to this nomination (see Appendix A).

Results

Appropriateness and Importance

This is an appropriate and important topic. Approximately one in four deaths in the United States is caused by heart disease,[2] and heart disease and stroke cost the U.S. nearly $1 billion each day due to medical costs and lost productivity.[8] Those at risk of developing CVD are often

prescribed blood pressure-lowering medication, cholesterol-lowering medication, and aspirin alone or in combination; however, long term adherence is poor.[3] Fixed-dose combination therapy has the potential to reduce the complexity of taking multiple medications, improve adherence, and lower costs.[5]

Fixed-dose combination therapy delivered as a polypill is not FDA-approved and not available in the U.S; however, the individual drugs in each class (aspirin, cholesterol-lowering agent, and blood pressure-lowering agent) are FDA-approved and have been recommended and used for secondary CVD prevention.

Desirability of New Review/Duplication

A new AHRQ evidence review examining fixed-dose combination therapy for CVD would not be duplicative of an existing product. We identified two systematic reviews[9,10] pertaining to the key question; however, these did not include the range of drug delivery options (ie, both as a single pill and separate pills) of interest, nor did they conduct analyses specific to the intervention-comparator pair (fixed-dose combination with aspirin, stain, and ACEI/ARB vs. management by a clinician) of interest. See Table 2, Duplication column for the systematic review citations that were determined to address the key questions.

Impact of a New Evidence Review

A new AHRQ systematic review on fixed-dose combination therapy for CVD may have high impact, as the value of fixed dose combination therapy for secondary prevention for CVD over management by a clinician is still debated.

Feasibility of a New Evidence Review

A new AHRQ evidence review examining fixed-dose combination therapy for CVD is not feasible at this time. We identified 4 RCTs,[5,7,11,12] 1 IPD meta-analysis,[13] 2 study protocols,[14,15] and 1 cost-analysis[16] of fixed-dose combination therapy delivered as a polypill. From our search of Clinicaltrials.gov we identified 2 ongoing studies[17,18] on fixed-dose combination therapy delivered as a polypill. We did not identify any completed or in-process studies examining fixed-dose combination therapy delivered as separate pills. See Table 2, Feasibility column for these citations.

Table 2. Key questions with the identified corresponding evidence reviews and original research

Key Question	Duplication (Completed or In-Process Evidence Reviews)	Feasibility (Published and Ongoing Research)
1. Effectiveness of fixed-dose combination therapy	Total number of completed or in-process evidence reviews: 1 • Cochrane: 1[9] • Other: 1[10]	<u>Size/scope of review</u> Single pill: 4 RCTs,[5,7,11,12] 1 IPD meta-analysis,[13] 2 study protocols,[14,15] and 1 cost-analysis[16] Separate pills: None identified. <u>ClinicalTrials.Gov</u> Single pill • 1 active, recruiting[17] • 1 active, not recruiting[18] Separate pills: none identified

Abbreviations: IPD=Individual Patient Data; RCT=Randomized Controlled Trial

Summary of Findings

- Appropriateness and importance: The nomination is both appropriate and important. Although CVD fixed dose-combination therapy delivered as a single pill (ie, the polypill) has not been approved by the FDA, each of the individual drugs have been approved separately.
- Duplication: A new review on this topic would not be duplicative of an existing product. We identified 2 reviews pertinent to the key question; however, these reviews did not include the range of drug delivery options of interest (ie, both as the polypill and separate pills), nor did they conduct analyses specific to the intervention-comparator pair of interest (fixed-dose combination with aspirin, stain, and ACEI/ARB vs. management by a clinician).
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Appendices

Appendix A: Selection Criteria Summary

Appendix B: Search Strategy & Results (Feasibility)

Appendix A. Selection Criteria Summary

Selection Criteria	Supporting Data
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	The polypill (ie, fixed-dose aspirin, BP-lowering medication, and cholesterol-lowering medication as a single pill) is not available in the U.S. However, fixed-dose combinations of these medications can be delivered together, such as in a blister pack.
1b. Is the nomination a request for a systematic review?	Yes, this topic is a request for a systematic review.
1c. Is the focus on effectiveness or comparative effectiveness?	The focus of this review is on effectiveness.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes, it is biologically plausible. Yes, it is consistent with what is known about the topic.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Yes, this topic represents a significant burden. Cardiovascular disease (CVD) is one of the leading causes of morbidity and mortality worldwide.[1] Those at risk of developing CVD are often prescribed blood pressure-lowering medication, cholesterol-lowering medication, and aspirin alone or in combination; however, long term adherence is poor.[3]
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes, this topic affects heath care decisions for a large population. Approximately 1 in 4 deaths in the United States is caused by heart disease.[2] Fixed-dose combination therapy has the potential to increase adherence and decrease adverse events from CVD.
2c. Represents important uncertainty for decision makers	Yes, this topic represents important uncertainty for decision makers.
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes, this nomination addresses both benefits and potential harms of fixed-dose combination treatment.
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes, this topic represents high costs to consumers, health care systems, and payers. Heart disease and stroke cost the U.S. nearly $1 billion each day due to medical costs and lost productivity.[8] Fixed-dose combination therapy has the potential to reduce the complexity of taking multiple medications, improve adherence, and lower costs.[5]
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	A new AHRQ review would not duplicate an existing product. We identified a 2014 Cochrane review[9] and an additional 2013 review[10] pertaining to the key question; however these reviews did not include the range of drug delivery options of interest (ie, both as the polypill and separate pills), nor did they conduct analyses specific to the intervention-comparator pair (fixed-dose combination with aspirin, stain, and ACEI/ARB vs. management by a clinician) of interest

4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Although it's clear that CVD patients should receive medications to lower BP and cholesterol, it's not clear whether fixed-dose treatment of 3 or more medications improves outcomes over management with individualized dose titration by a health care practitioner.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes, there is evidence of practice variation in the secondary prevention of CVD events among CVD patients.[19,20]
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	A new AHRQ review is not feasible at this time. Size/scope of the review: We identified 4 RCTs,[5,7,11,12] 1 IPD meta-analysis,[13] 2 study protocols,[14,15] and 1 cost-analysis [16] of the polypill. We did not identify any studies that delivered the 3 medications separately. Clinicaltrials.gov: We identified 2 ongoing studies[17,18] of the polypill. We did not identify any studies that delivered the 3 medications separately.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; BP= Blood pressure; CVD=Cardiovascular disease IPD= Individual patient data; RCT=Randomized controlled trial

Appendix B. Search Strategy & Results (Feasibility)

Topic: PolyPill for CVD Date: December 21, 2016 Database Searched: MEDLINE (PubMed)	
Concept	Search String
PolyPill	(polypill[Title/Abstract] OR pollypill[Title/Abstract] OR poly-pill[Title/Abstract] OR polly-pill[Title/Abstract] OR poly pill[Title/Abstract] OR polly pill[Title/Abstract]) OR bundled therapy[Title/Abstract] OR fixed-dose combination[Title/Abstract] OR blister pack[Title/Abstract] OR polypack[Title/Abstract] OR Aspirin, Dipyridamole Drug Combination"[Mesh] OR "Drug Combinations"[Majr]
AND	
Cardiovascular Diseases	"Cardiovascular Diseases/drug therapy"[Mesh]
NOT	
Not Editorials, etc.	((((((("Letter"[Publication Type]) OR "News"[Publication Type]) OR "Patient Education Handout"[Publication Type]) OR "Comment"[Publication Type]) OR "Editorial"[Publication Type])) OR "Newspaper Article"[Publication Type]
Limit to last 5 years ; human ; English ;	Filters activated: published in the last 5 years, Humans, English
N=157	
Systematic Review	PubMed subsection “Systematic [sb]”
Randomized Controlled Trials	Cochrane Sensitive Search Strategy for RCT’s “(((((((((groups[tiab])) OR (trial[tiab])) OR (randomly[tiab])) OR (drug therapy[sh])) OR (placebo[tiab])) OR (randomized[tiab])) OR (controlled clinical trial[pt])) OR (randomized controlled trial[pt])”
Other	

Clinicaltrials.gov
4 studies found for: polypill | Studies received from 12/21/2011 to 12/21/2016
https://clinicaltrials.gov/ct2/results?term=polypill&type=&rslt=&recr=&age_v=&gndr=&cond=&intr=&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=12%2F21%2F2011&rcv_e=12%2F21%2F2016&lup_s=&lup_e=